(FILE 'HOME' ENTERED AT 14:50:17 ON 06 JUL 2001)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS, SCISEARCH' ENTERED AT 14:50:31 ON 06 JUL 2001

L1 49 S ADENOVIR? AND GUTLESS
L2 369565 S IMMUNE RESPONSE OR IMMUNOGENIC?
L3 23 S L1 AND L2
L4 9 DUPLICATE REMOVE L3 (14 DUPLICATES REMOVED)
L5 61 S HELPER DEPENDENT AND ADENOVIR? AND L2
L6 52 S L5 NOT L3
L7 21 DUPLICATE REMOVE L6 (31 DUPLICATES REMOVED)
L8 95 S READMINISTRATION AND ADENOVIR? AND HUMORAL
L9 86 S L8 NOT L3 NOT L5
L10 24 DUPLICATE REMOVE L9 (62 DUPLICATES REMOVED)
L11 10 S NEUTRALIZING AND L2 AND PROBLEMS AND ADENOVIR?
L12 3 DUPLICATE REMOVE L11 (7 DUPLICATES REMOVED)
L13 6 S WILSON?/AU AND REVIEW? AND ADENOVIR? AND IMMUN?
L14 6 DUPLICATE REMOVE L13 (0 DUPLICATES REMOVED)
L15 82 S ADENOVIR? AND PARTICLE AND HUMORAL AND IMMUN?
L16 77 S L15 NOT L8 NOT L3 NOT L5
L17 77 S L15 NOT L8
L18 77 S L17 NOT L3
L19 77 S L18 NOT L5
L20 24 DUPLICATE REMOVE L19 (53 DUPLICATES REMOVED)
L21 0 S ADENOVIR? WITH PROBLEMS WITH IMMUN?
L22 29 S ADENOVIR?(S)PROBLEMS(S)IMMUN?(S)(HUMORAL OR NEUTRALIZ?)
L23 25 S L22 NOT L15 NOT L8 NOT L5 NOT L3
L24 9 DUPLICATE REMOVE L23 (16 DUPLICATES REMOVED)

L7 ANSWER 17 OF 21 MEDLINE DUPLICATE 6
TI An ***adenoviral*** vector deleted for all viral coding sequences results in enhanced safety and extended expression of a leptin transgene.
AN 1998318577 MEDLINE
DN 98318577 PubMed ID: 9653106
TI An ***adenoviral*** vector deleted for all viral coding sequences results in enhanced safety and extended expression of a leptin transgene.
AU Morsy M A; Gu M; Motzel S; Zhao J; Lin J; Su Q; Allen H; Franlin L; Parks R J; Graham F L; Kochanek S; Bett A J; Caskey C T
CS Department of Human Genetics, Merck Research Laboratories, West Point, PA 19486, USA.. morsy@merck.com
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Jul 7) 95 (14) 7866-71.
Journal code: PV3; 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980817
Last Updated on STN: 20000303
Entered Medline: 19980806
AB ***Adenoviral*** (Ad)-mediated in vivo gene transfer and expression are limited in part by cellular ***immune*** ***responses*** to viral-encoded proteins and/or transgene ***immunogenicity*** . In an attempt to diminish the former responses, we have previously developed and described ***helper*** - ***dependent*** (HD) Ad vectors in which the viral protein coding sequences are completely eliminated. These HD vectors have up to 37 kb insert capacity, are easily propagated in a Cre recombinase-based system, and can be produced to high concentration and purity (>99.9% helper-free vector). In this study, we compared safety and efficacy of leptin gene delivery mediated by an HD vector (HD-leptin) and a first-generation E1-deleted Ad vector (Ad-leptin) in normal lean and ob/ob (leptin-deficient) mice. In contrast to evidence of liver toxicity, inflammation, and cellular infiltration observed with Ad-leptin delivery in mice, HD-leptin delivery was associated with a significant improvement in associated safety/toxicity and resulted in efficient gene delivery, prolonged elevation of serum leptin levels, and associated weight loss. The greater safety, efficient gene delivery, and increased insert capacity of HD vectors are significant improvements over current Ad vectors and represent favorable features especially for clinical gene therapy applications.

L7 ANSWER 16 OF 21 MEDLINE DUPLICATE 5
TI Expanded-capacity ***adenoviral*** vectors--the ***helper*** - ***dependent*** vectors.
AN 1999188120 MEDLINE
DN 99188120 PubMed ID: 10088128
TI Expanded-capacity ***adenoviral*** vectors--the ***helper*** - ***dependent*** vectors.
AU Morsy M A; Caskey C T
CS Dept of Human Genetics, Merck & Co., Inc., West Point, PA 19486, USA.. morsy@merck.com
SO MOLECULAR MEDICINE TODAY, (1999 Jan) 5 (1) 18-24. Ref: 40

Journal code: CMK; 9508560. ISSN: 1357-4310.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990511
AB Significant advances have recently been made in the development of vectors and gene-delivery systems for gene therapy. Experiments performed over the past decade have revealed how vectors will have to be modified to make them a clinically viable treatment option. In the case of ***adenovirus*** (Ad) vectors, which have been particularly useful as gene delivery vehicles, the main drawback associated with their use is vector-mediated ***immunogenicity*** . Recent modifications of the Ad backbone have led to the development of ***helper*** - ***dependent*** (HD) Ad vectors, which are completely devoid of all viral protein-coding sequences. These modifications have significantly reduced the ***immunogenicity*** of Ad vectors and have enhanced their safety. It is expected that HD vectors will become important tools for future clinical gene therapy.

L7 ANSWER 15 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
TI Use of ***helper*** - ***dependent*** ***adenoviral*** vectors of alternative serotypes permits repeat vector administration
AN 1999:717964 SCISEARCH
GA The Genuine Article (R) Number: 236KP
TI Use of ***helper*** - ***dependent*** ***adenoviral*** vectors of alternative serotypes permits repeat vector administration
AU Parks R J; Evelegh C M; Graham F L (Reprint)
CS OTTAWA GEN HOSP, RES INST, CTR MOL MED, 501 SMYTH RD, OTTAWA, ON K1H 8L6, CANADA (Reprint); MCMASTER UNIV, DEPT BIOL, HAMILTON, ON L8S 4K1, CANADA; MCMASTER UNIV, DEPT PATHOL, HAMILTON, ON L8S 4K1, CANADA
CYA CANADA
SO GENE THERAPY, (SEP 1999) Vol. 6, No. 9, pp. 1565-1573.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0969-7128.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 74
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We have developed a new helper ***adenovirus*** (Ad) based on serotype 2, Ad2LCBcCARP, for use in the Cre/loxP system (Parks et al. Proc Natl Acad Sci USA, 1996; 93: 13565-13570) to generate Ad vectors deleted of all protein coding sequences (***helper*** - ***dependent*** Ad vectors (hdAd)). A comparison of Ad2LC8cCARP and our original helper Virus (based on serotype 5, Ad5LC8cluc) showed that the two helper viruses amplified hdAd with a similar efficiency, and resulted in a similar yield and purify after large-scale preparation of vector In vitro, the resulting hdAd2 had a similar transduction efficiency and expression kinetics of

transgene (beta-gal) as the hdAdS. An important feature of the ***helper*** - ***dependent*** system is that all virion components, except the virion DNA, derive from the helper virus. Consequently, vectors produced with help from Ad2LC8cCARP were not neutralized by antibodies against Ad5, and vectors produced with Ad5 helper were resistant to neutralizing antibodies against Ad2. Analysis of transgene expression in mouse liver after intravenous injection of the Ad2-based hdAd showed that the vector could efficiently transduce the liver, and produce high levels of a foreign transgene, similar to those expressed by the hdAd generated with the Ad5 helper virus. Mice immunized with hdAd2 produced Ad2-neutralizing antibodies, which did not crossreact with hdAdS. To determine if successful repeat Ad vector administration could be achieved by sequential use of alternative Ad serotypes, we injected mice with hdAd2 (hSEAP) followed 3 months later by a lacZ-expressing hdAd of either the same or different serotype. Repeated administration of hdAd2 resulted in a 30- to 100-fold reduction in transgene expression compared with naive animals. In contrast no decrease in transgene expression was observed when the second vector was of a different serotype. These results demonstrate that effective vector readministration can be achieved by the sequential use of hdAds based on alternative serotypes.

L7 ANSWER 11 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
TI Toxicity associated with repeated administration of first-generation ***adenovirus*** vectors does not occur with a ***helper*** - ***dependent*** vector
AN 2000:482738 SCISEARCH
GA The Genuine Article (R) Number: 327MD
TI Toxicity associated with repeated administration of first-generation ***adenovirus*** vectors does not occur with a ***helper*** - ***dependent*** vector
AU ONeal V K (Reprint); Zhou H S; Morral N; Langston C; Parks R J; Graham F L; Kochanek S; Beaudet A L
CS UNIV N CAROLINA, CYST FIBROSIS PULM RES & TREATMENT CTR, 7011 THURSTON BOWLES BLDG, CB 7248, CHAPEL HILL, NC 27599 (Reprint); BAYLOR COLL MED, DEPT MOL & HUMAN GENET, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT PATHOL, HOUSTON, TX 77030; MCMASTER UNIV, DEPT BIOL, HAMILTON, ON, CANADA; MCMASTER UNIV, DEPT PATHOL, HAMILTON, ON, CANADA
CYA USA; CANADA
SO MOLECULAR MEDICINE, (MAR 2000) Vol. 6, No. 3, pp. 179-195.
Publisher: JOHNS HOPKINS UNIV PRESS, JOURNALS PUBLISHING DIVISION, 2715 NORTH CHARLES ST, BALTIMORE, MD 21218-4319.
ISSN: 1076-1551.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 80
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: Certain gene therapy protocols may require multiple administrations of vectors to achieve therapeutic benefit to the patient. This may be especially relevant for vectors such as ***adenoviral*** vectors that do not integrate into the host chromosome. Because immunocompetent animal models used for gene transfer studies develop neutralizing antibodies to ***adenoviral*** vectors after a single administration, little is known about how repeat administrations of vectors might affect transgene expression and vector toxicity.

Materials and Methods: We used mice deficient in the membrane spanning region of immunoglobulin (IgM), which do not develop antibodies, to evaluate the effect of repeated intravenous administration of first-generation and ***helper*** - ***dependent*** ***adenoviral*** vectors expressing human alpha(1)-antitrypsin (hAAT). The duration and levels of transgene expression were evaluated after repeated administration of vectors. Toxicity was assessed by measuring the level of liver enzymes in the serum and the degrees of hepatocyte hypertrophy and proliferation.

Results: We found that previous administration of first-generation ***adenoviral*** vectors can alter the response to subsequent doses. These alterations included an increase in transgene expression early (within 1 and 3 days), followed by a rapid drop in expression by day 7. In addition, previous administrations of first-generation vectors led to an increase in toxicity of subsequent doses, as indicated by a rise in liver enzymes and an increase in hepatocyte proliferation. In contrast to first-generation vectors, use of the ***helper*** - ***dependent*** ***adenovirus*** vector, Ad-STK109, which contained no viral coding regions, did not lead to increased toxicity after multiple administrations.

Conclusions: We conclude that the response of the host to ***adenoviral*** vectors can be altered after repeated administration, compared with the response after the initial vector dose. In addition, these experiments provide further evidence for the relative safety of ***helper*** - ***dependent*** ***adenoviral*** vectors for gene therapy, compared with first-generation vectors.

L7 ANSWER 7 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
TI Prolonged expression and effective readministration of erythropoietin delivered with a fully deleted ***adenoviral*** vector
AN 2000:287987 SCISEARCH
GA The Genuine Article (R) Number: 302RF
TI Prolonged expression and effective readministration of erythropoietin delivered with a fully deleted ***adenoviral*** vector
AU Maione D; Wiznerowicz M; Delmastro P; Cortese R; Ciliberto G; LaMonica N; Savino R (Reprint)
CS IST RIC BIOL MOL P ANGELETTI, DEPT GENET, VIA PONTINA KM 30, 600, I-00040 POMEZIA, ITALY (Reprint); IST RIC BIOL MOL P ANGELETTI, DEPT GENET, I-00040 POMEZIA, ITALY; GREAT POLAND CANC CTR, UNIV SCH MED SCI, DEPT CANC IMMUNOL, PL-61866 POZNAN, POLAND
CYA ITALY; POLAND
SO HUMAN GENE THERAPY, (10 APR 2000) Vol. 11, No. 6, pp. 859-868.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 1043-0342.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 52
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB ***Helper*** - ***dependent*** (HD) ***adenoviral*** (Ad) vectors, in which all viral coding sequences are deleted, have been generated. We show here that intravenous delivery of a mouse EPO (mEPO) expression cassette cloned in an HD vector in immunocompetent mice is effective and long lasting, but not permanent. A precise dose-response relationship between the dose of injected virus and stable EPO serum

levels was observed, together with a 100-fold increase in gene expression per infectious particle when compared with a first-generation Ad vector bearing the same cassette. As a direct consequence, therapeutic increases in hematocrit that lasted more than 6 months were achieved with minute amounts of virus, which caused no detectable production of neutralizing antibodies. Intravenous readministration of the HD-mEPO vector in the same mice was as effective as in naive animals without any need for prior immunosuppression. Finally, HD-mEPO injection in subtotally nephrectomized rats improved the anemic status induced by surgery. HD Ad vectors are thus excellent tools for EPO gene therapy.

L10 ANSWER 24 OF 24 MEDLINE DUPLICATE 19
TI Recombinant IL-12 prevents formation of blocking IgA antibodies to recombinant ***adenovirus*** and allows repeated gene therapy to mouse lung.
AN 96071593 MEDLINE
DN 96071593 PubMed ID: 7585213
TI Recombinant IL-12 prevents formation of blocking IgA antibodies to recombinant ***adenovirus*** and allows repeated gene therapy to mouse lung.
CM Comment in: Nat Med. 1995 Sep;1(9):887-9
AU Yang Y; Trinchieri G; Wilson J M
CS Institute for Human Gene Therapy, Wistar Institute, University of Pennsylvania Medical Center, Philadelphia 19104-4268, USA.
SO NATURE MEDICINE, (1995 Sep) 1 (9) 890-3.
Journal code: CG5; 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228
AB Enthusiasm for the use of recombinant ***adenoviruses*** in gene therapy has been tempered by the problematic immune responses that develop to the virus and virus-infected cells. ***Humoral*** immune responses to the input viral proteins generate neutralizing antibodies that thwart attempts to effectively administer the therapy more than once. Previous studies in murine models of gene therapy for cystic fibrosis (CF) have shown that the formation of ***adenoviral*** antibodies of the IgA subtype, a process that is dependent on T helper cells of the TH2 subset, contributes to a block in gene transfer that occurs following a second administration of virus. We show in this report that coadministration of interferon-gamma (IFN-gamma) (or interleukin-12, which activates TH1 cells to secrete IFN-gamma) with the recombinant ***adenovirus*** into the airway of C57BL/6 mice diminishes the activation of TH2 cells and formation of neutralizing antibody, allowing for efficient ***readministration*** of recombinant virus. This suggests a strategy for gene therapy of CF in which administration of a short-acting immune modulator at the time of gene therapy may be sufficient to overcome the problems of ***humoral*** immunity.

L10 ANSWER 21 OF 24 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Gene therapy with recombinant ***adenovirus*** vectors: Evaluation of the host immune response.
AN 97228250 EMBASE
DN 1997228250
TI Gene therapy with recombinant ***adenovirus*** vectors: Evaluation of the host immune response.
AU Christ M.; Lusky M.; Stoeckel F.; Dreyer D.; Dieterle A.; Michou A.- I.; Pavirani A.; Mehtali M.
CS M. Christ, Transgene, SA, 11 rue de Molsheim, 67082 Strasbourg, Cedex, France
SO Immunology Letters, (1997) 57/1-3 (19-25).

Refs: 36
ISSN: 0165-2478 CODEN: IMLED6
PUI S 0165-2478(97)00049-7
CY Netherlands
DT Journal; Conference Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB E1, E3-deleted, replication-deficient recombinant ***adenoviruses*** are widely studied as vectors for their capacity to transfer therapeutic genes in vivo. They can infect a wide variety of dividing and quiescent cells from different organs and possess a large packaging capacity. One of the major limitations in the use of these vectors for gene therapy is the transient expression of the transgene in vivo and the poor transduction efficiency when re-administered. Despite the deletion of the viral E1 region, low level of early and late viral genes are expressed in vivo. Thus, vital antigens plus those derived from transgene expression in transduced cells contribute to cellular immune responses leading to the destruction of these cells. Production of anti- ***adenovirus*** antibodies, the cellular immune response as well as the early non-specific clearance of the vectors, constitute barriers to successful gene therapy. New vectors have been derived with additional deletions in the E2a or the E4 regions. Such second generation vectors were evaluated in vivo. These studies have revealed the complexity of the immune mechanisms elicited by these vectors and the importance of several parameters in these evaluations (i.e. mouse strains, nature of the transgene, route of administration...). In order to inhibit the production of neutralizing antibodies to ***adenovirus*** that prevent from further ***readministration*** of the vectors, immunosuppressive strategies were undertaken. Treatment regimens with immunosuppressive drugs (cyclophosphamide, FK506) or with monoclonal antibodies that block either the T cell receptor or costimulation pathways allow prolonged transgene expression and/or ***readministration*** of ***adenoviral*** vectors. In addition, transduction efficiencies may be increased by transiently inhibiting non-specific immune mechanisms that lead to the dramatic early clearance of the vectors. Taken together, these strategies may improve further gene therapy protocols by decreasing the host immune response to ***adenoviral*** vectors.

L10 ANSWER 19 OF 24 MEDLINE DUPLICATE 15
TI Transient immunosuppression with deoxyspergualin improves longevity of transgene expression and ability to readminister ***adenoviral*** vector to the mouse lung.
AN 97333607 MEDLINE
DN 97333607 PubMed ID: 9189767
TI Transient immunosuppression with deoxyspergualin improves longevity of transgene expression and ability to readminister ***adenoviral*** vector to the mouse lung.
AU Kaplan J M; Smith A E
CS Genzyme Corporation, Framingham, MA 01701-9322, USA.
SO HUMAN GENE THERAPY, (1997 Jun 10) 8 (9) 1095-104.
Journal code: A12; 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199708
ED Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970827
AB Animal studies have suggested that the clinical usefulness of recombinant ***adenoviruses*** (Ad) as vectors for therapeutic gene delivery may be limited by their immunogenicity. Neutralizing antibodies elicited by capsid proteins reduce the efficiency of vector ***readministration*** whereas cytotoxic T lymphocytes (CTLs) directed against viral proteins and/or immunogenic transgene products expressed by transfected cells have the potential to limit persistence of expression. In this study, transient administration of the novel immunosuppressant deoxyspergualin (DSG) was found to inhibit the development of both ***humoral*** and cell-mediated immune responses against Ad vector delivered intranasally. DSG treatment of primed mice previously exposed to wild-type Ad impaired the development of antibodies in response to a secondary and even tertiary challenge with Ad vector. As a result, improved gene transfer was obtained upon subsequent administration of a beta-galactosidase (beta-Gal)-encoding Ad vector. Short-term administration of DSG also depressed the activation of CD4+ and CD8+ T lymphocytes as assessed by measurement of antigen-specific proliferation and CTL activity, respectively. The marked suppression of CTL activity against Ad vector in DSG-treated mice correlated with improved persistence of transgene expression in the lung.

L20 ANSWER 20 OF 24 MEDLINE DUPLICATE 13
TI ***Humoral*** ***immune*** response to the capsid components of recombinant ***adenoviruses*** : routes of ***immunization*** modulate virus-induced Ig subclass shifts.
AN 97234531 MEDLINE
DN 97234531 PubMed ID: 9079805
TI ***Humoral*** ***immune*** response to the capsid components of recombinant ***adenoviruses*** : routes of ***immunization*** modulate virus-induced Ig subclass shifts.
AU Gahery-Segard H; Juillard V; Gaston J; Lengagne R; Pavirani A; Boulanger P; Guillet J G
CS Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM Unite 445, Universite R. Descartes, Paris, France.. gahery@icgm.cochin.inserm.fr
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Mar) 27 (3) 653-9. Journal code: EN5; 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 19970507
Last Updated on STN: 20000907
Entered Medline: 19970429
AB This study examines in detail the capsid-specific ***humoral*** ***immune*** response of BALB/c mice after one single injection of a replication-defective ***adenovirus*** . Two routes of ***immunization*** , intravenous (i.v.) and intraperitoneal (i.p.), were compared for the response induced against the ***adenovirus*** ***particle*** and the three major components of the viral capsid,

hexon, penton base, and fiber. A single ***immunization*** with the replication-defective ***adenovirus*** induces a long and persistent ***humoral*** response specific for the virus. However, the molecular components of the viral capsid are differentially recognized depending on the route of ***immunization*** . The sera from mice ***immunized*** i.p. recognized only the hexon protein and a preferential switch to the IgG2a subclass was obtained which remained stable 100 days post-***immunization*** . The sera obtained from mice ***immunized*** i.v. gave a more complex response. At the beginning of the response, an isotype bias toward the IgG2a subclass was observed, but the isotype distribution changed during the whole period of the response. Neutralizing activity was maximum 45 days after ***immunization*** by both routes, and no activity was detectable after 3 months. However, the i.v. serum displayed a higher neutralizing activity than the i.p. serum. The IgM antiviral antibodies appeared to be an important component of the neutralizing activity, and the two routes of ***immunization*** do not induce the same IgG isotypes to neutralize viral infectivity. Extension of these findings to human gene therapy using recombinant ***adenoviruses*** may help to characterize the precise viral protein targets of neutralizing antibodies.

L20 ANSWER 16 OF 24 MEDLINE DUPLICATE 11
TI ***Immune*** response to recombinant capsid proteins of ***adenovirus*** in humans: antifiber and anti-penton base antibodies have a synergistic effect on neutralizing activity.
AN 1998139139 MEDLINE
DN 98139139 PubMed ID: 9499099
TI ***Immune*** response to recombinant capsid proteins of ***adenovirus*** in humans: antifiber and anti-penton base antibodies have a synergistic effect on neutralizing activity.
AU Gahery-Segard H; Farace F; Godfrin D; Gaston J; Lengagne R; Tursz T; Boulanger P; Guillet J G
CS Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM Unite 445, Institut Cochin de Genetique Moleculaire, Universite R. Descartes, Hopital Cochin, Paris, France.. gahery@icgm.cochin.inserm.fr
SO JOURNAL OF VIROLOGY, (1998 Mar) 72 (3) 2388-97.
Journal code: KCV; 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
ED Entered STN: 19980319
Last Updated on STN: 20000824
Entered Medline: 19980312
AB Replication-deficient ***adenovirus*** used in humans for gene therapy induces a strong ***immune*** response to the vector, resulting in transient recombinant protein expression and the blocking of gene transfer upon a second administration. Therefore, in this study we examined in detail the capsid-specific ***humoral*** ***immune*** response in sera of patients with lung cancer who had been given one dose of a replication-defective ***adenovirus*** . We analyzed the ***immune*** response to the three major components of the viral capsid, hexon (Hx), penton base (Pb), and fiber (Fi). A longitudinal study of the ***humoral*** response assayed on ***adenovirus*** ***particle***

-coated enzyme-linked ***immunosorbent*** assay plates showed that patients had preexisting ***immunity*** to ***adenovirus*** prior to the administration of ***adenovirus*** -beta-gal. The level of the response increased in three patients after ***adenovirus*** administration and remained at a maximum after three months. One patient had a strong ***immune*** response to ***adenovirus*** prior to treatment, and this response was unaffected by ***adenovirus*** administration. Sera collected from the patients were assayed for recognition of each individual viral capsid protein to determine more precisely the molecular basis of the ***humoral*** ***immune*** response. Clear differences existed in the ***humoral*** response to the three major components of the viral capsid in serum from humans. Sequential appearance of these antibodies was observed: anti-Fi antibodies appeared first, followed by anti-Pb antibodies and then by anti-Hx antibodies. Moreover, anti-Fi antibodies preferentially recognized the native trimeric form of Fi protein, suggesting that they recognized conformational epitopes. Our results showed that sera with no neutralizing activity contained only anti-Fi antibodies. In contrast, neutralizing activity was only obtained with sera containing anti-Fi and anti-Pb antibodies. More importantly, we showed that anti-native Fi and anti-Pb antibodies had a synergistic effect on neutralization. The application of these conclusions to human gene therapy with recombinant ***adenovirus*** should lead to the development of strategies to overcome the formation of such neutralization antibodies, which have been shown to limit the efficacy of gene transfer in humans.

L20 ANSWER 10 OF 24 MEDLINE DUPLICATE 7
TI Variability of human systemic ***humoral*** ***immune*** responses to ***adenovirus*** gene transfer vectors administered to different organs.
AN 1999329198 MEDLINE
DN 99329198 PubMed ID: 10400771
TI Variability of human systemic ***humoral*** ***immune*** responses to ***adenovirus*** gene transfer vectors administered to different organs.
AU Harvey B G; Hackett N R; El-Sawy T; Rosengart T K; Hirschowitz E A; Lieberman M D; Lesser M L; Crystal R G
CS Division of Pulmonary and Critical Care Medicine, Weill Medical College of Cornell University-New York Presbyterian Hospital, New York, USA.
NC MO1RR00047 (NCRR)
PO1 HL51746 (NHLBI)
R21 CA75153 (NCI)
+
SO JOURNAL OF VIROLOGY, (1999 Aug) 73 (8) 6729-42.
Journal code: KCV; 0113724. ISSN: 0022-538X.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990824
AB Administration of ***adenovirus*** (Ad) vectors to

immunologically naive experimental animals almost invariably results in the induction of systemic anti-Ad neutralizing antibodies. To determine if the human systemic ***humoral*** host responses to Ad vectors follow a similar pattern, we evaluated the systemic (serum) anti-Ad serotype 5 (Ad5) neutralizing antibodies in humans after administration of first generation (E1(-) E3(-)) Ad5-based gene transfer vectors to different hosts. AdGVCFTR.10 (carrying the normal human cystic fibrosis [CF] transmembrane regulator cDNA) was sprayed (8 x 10(7) to 2 x 10(10) ***particle*** units [PU]) repetitively (every 3 months or every 2 weeks) to the airway epithelium of 15 individuals with CF. AdGVCD.10 (carrying the Escherichia coli cytosine deaminase gene) was administered (8 x 10(8) to 8 x 10(9) PU; once a week, twice) directly to liver metastasis of five individuals with colon cancer and by the intradermal route (8 x 10(7) to 8 x 10(9) PU, single administration) to six healthy individuals. AdGVVEGF121.10 (carrying the human vascular endothelial growth factor 121 cDNA) was administered (4 x 10(8) to 4 x 10(9.5) PU, single administration) directly to the myocardium of 11 individuals with ischemic heart disease. Ad vector administration to the airways of individuals with CF evoked no or minimal serum neutralizing antibodies, even with repetitive administration. In contrast, intratumor administration of an Ad vector to individuals with metastatic colon cancer resulted in a robust antibody response, with anti-Ad neutralizing antibody titers of 10(2) to >10(4). Healthy individuals responded to single intradermal Ad vector variably, from induction of no neutralizing anti-Ad antibodies to titers of 5 x 10(3). Likewise, individuals with ischemic heart disease had a variable response to single intramyocardial vector administration, ranging from minimal neutralizing antibody levels to titers of 10(4). Evaluation of the data from all trials showed no correlation between the peak serum neutralizing anti-Ad response and the dose of Ad vector administered ($P > 0.1$, all comparisons). In contrast, there was a striking correlation between the peak anti-Ad5 neutralizing antibody levels evoked by vector administration and the level of preexisting anti-Ad5 antibodies ($P = 0.0001$). Thus, unlike the case for experimental animals, administration of Ad vectors to humans does not invariably evoke a systemic anti-Ad neutralizing antibody response. In humans, the extent of the response is dictated by preexisting antibody titers and modified by route of administration but is not dose dependent. Since the extent of anti-Ad neutralizing antibodies will likely modify the efficacy of administration of Ad vectors, these observations are of fundamental importance in designing human gene therapy trials and in interpreting the efficacy of Ad vector-mediated gene transfer.

L24 ANSWER 5 OF 9 MEDLINE DUPLICATE 5
TI Cyclophosphamide diminishes inflammation and prolongs transgene expression following delivery of adenoviral vectors to mouse liver and lung.
AN 97018140 MEDLINE
DN 97018140 PubMed ID: 8864756
TI Cyclophosphamide diminishes inflammation and prolongs transgene expression following delivery of adenoviral vectors to mouse liver and lung.
AU Jooss K; Yang Y; Wilson J M
CS Institute for Human Gene Therapy, University of Pennsylvania, Philadelphia, USA.
SO HUMAN GENE THERAPY, (1996 Aug 20) 7 (13) 1555-66. Journal code: A12; 9008950. ISSN: 1043-0342.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970102
AB ***Immune*** responses to ***adenovirus*** -mediated gene transfer contribute to the ***problems*** of transient recombinant gene expression, inflammation, and difficulties with vector readministration. Activation of CD4+ T cells is required for full realization of effector function of both CD8+ T cells (i.e., cytotoxic T cells) and B cells (i.e., ***neutralizing*** antibody). We evaluate in this study the effectiveness of a short course of high-dose cyclophosphamide to block ***immune*** responses in mice administered vector into lung and liver of C57BL/6 mice. Administration of cyclophosphamide with vector directed to liver blocked activation and mobilization of both CD4+ and CD8+ T cells. As a result, transgene expression was prolonged, inflammation was reduced, and, at the higher doses of cyclophosphamide, formation of ***neutralizing*** antibody was prevented and the vector was successfully readministered. Similar studies in the lung demonstrated an effective blockade of T and B cell responses. In contrast to the liver, where it was easier to stabilize transgene expression than to prevent ***neutralizing*** antibody, cyclophosphamide prevented the formation of ***neutralizing*** antibodies at all doses in the lung, whereas stabilization of transgene expression was only achieved at the highest dose. These experiments begin to define the parameters by which cyclophosphamide could be used as an adjunct in gene therapy.

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TI Ovine adenovirus vectors overcome preexisting humoral immunity against human adenoviruses in vivo.
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AB Recombinant human ***adenoviruses*** (hAd) have become widely used as tools to achieve efficient gene transfer. However, successful application of hAd-derived vectors in clinical trials is limited due to ***immunological*** and potential safety ***problems*** inherent in their human origin. In this study, we describe a recombinant ovine ***adenovirus*** (OAV) as an alternative vector for gene transfer in

vivo. In contrast to an hAd vector, the OAV vector was not ***neutralized*** by human sera. An OAV vector which contained the cDNA of the human alpha1-antitrypsin (hAAT) gene linked to the Rous sarcoma virus promoter was generated and administered systemically to mice. The level and duration of hAAT gene expression was similar to that achieved with an hAd counterpart in both ***immunocompetent*** and ***immunodeficient*** mice. However, the tissue distribution of the OAV vector differed from that observed for hAd vectors in that the liver was not the dominant target. Significantly, we demonstrated efficient gene transfer with the OAV vector into mice ***immunized*** with hAd vectors and vice versa. We also confirm that the ***immune*** response to a transgene product can prevent its functional expression following sequential application of a vector. Our results suggest a possible solution to endemic ***humoral*** ***immunity*** against currently used hAd vectors and should therefore have an impact on the design of improved gene therapy protocols utilizing ***adenovirus*** vectors.